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FORMATION WITHIN SENSORY NUCLEUS V OF SYNAPTIC ASSOCIATIONS MEDIATING CUTANEOUS LOCALIZATION

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FIVE FIGURES

Tactile stimulation of different cutaneous points about the head and face region in the blind decerebrate salamander or newt evokes different types of withdrawal responses adapted in each instance to the cutaneous area stimulated. Stimulation of the top of the snout, for example, causes depression of the head, whereas the same stimulus applied under the chin causes elevation. Stimulation around the eye evokes withdrawal of the eyeball. Stimulation of the side of the jaw results in sideward withdrawal of the head. Stimuli applied to intermediate points may arouse intermediate reactions such as combined sideward and downward withdrawal of the head. These withdrawal responses with their local sign properties occur also in frogs and toads. The anurans, however, more commonly respond with wiping reactions of the ipsilateral forelimb which, even more than the withdrawal reactions, are differentially aimed with reference to the particular cutaneous points stimulated.

The various sensory fibers of the trigeminal nerve mediating these reflexes must acquire specific central associations selectively adjusted to the cutaneous loci supplied in the periphery. The present investigation is concerned with the problem of how these orderly relations between sensory cutaneous field and brain centers become established. A priori there are three possibilities: First, the organization

might be the outcome of some functional type of adaptation akin to learning whereby the central associations become adjusted through activity in accordance with the adaptiveness of their functional effects. Secondly, the central-peripheral relations might be patterned directly in growth through some orderly plan in the spacing and timing of events in neurogenesis such that fibers entering the sensory nucleus V from different cutaneous areas become automatically directed by mechanical forces to appropriate central terminals. Or, thirdly, the sensory fibers might form the proper reflex relations in a predetermined manner on the basis of selective physicochemical affinities between the central and sensory neurons. The third explanation has found support in earlier experiments on the development of cutaneous local sign in the hind limb area of the frog (Sperry, '49). The following observations on synaptic formation in the sensory V nuclei under various experimental conditions likewise appear to rule out the first two of the above a priori possibilities in favor of the third.

EXPERIMENTAL PLAN AND METHODS

First tested was the effect upon cutaneous localization of section and regeneration of nerve root V. The original spatial arrangement of fiber pathways into the brain becomes completely disrupted during regeneration. Hence a recovery of the normal reflexes would show that the patterning of central linkages is not dependent upon a special schedule and spatial arrangement in the ingrowth of the sensory root fibers. As a more severe test of this point, root V was cross-united to root VII so that the regenerating V fibers entered the brain over the pathways of VII.

The role of functional adjustment was tested by means of surgical alterations which served to make the usual central patterns functionally maladaptive. The peripheral ophthalmic branch of the trigeminal nerve was crossed in urodeles into the mandibular branch prior to or during regeneration of the nerve root V. Establishment of the us-

ual synaptic pattern under these circumstances would cause the animals to push against rather than to withdraw from an irritating stimulus applied under the jaw. Also in frog tadpoles the ophthalmic nerve branch was crossed into the contralateral ophthalmic nerve prior to emergence of the forelimbs. Should the central reflex patterns undergo maturation in their usual way, the metamorphosed frogs should wipe at the wrong side of the face upon stimulation in the ophthalmic area. Maladaptive results like the foregoing would rule out functional adaptation as the organizing factor. Conversely, recovery of normal reactions in the face of these anatomical alterations would strongly support functional adaptation as the element of major importance.

If the sensory fibers should form their typical central relations under all these test conditions, i.e., despite haphazard intermixing and deflection of fibers into atypical pathways and despite maladaptiveness of the functional effects, it would indicate that fibers innervating different cutaneous areas differ in character and are predestined by their specificity to form particular kinds of central reflex associations.

The animals used were Triturus viridescens, the common crimson-spotted newt in the terrestrial eft and adult aquatic phases, and also tadpole and adult anurans of several different species as indicated below in context. All operations were performed with watchmaker's forceps and fine scissors under a dissecting microscope following anesthetization of the animals with ether and/or urethane. Decerebration posterior to the optic chiasma was routinely carried out previous to the final tests of function in order to calm the animals and to eliminate vision. In many cases the roots or peripheral branches of neighboring nerves, the cutaneous innervation of which overlapped that of the test nerve, were also sectioned prior to the final tests. The reflexes were elicited by touching various cutaneous points with the tip of a fine copper wire (gauge no. 35) 4 cm long, coiled at its base and mounted on a stylus. The wire was applied with pressures which ranged up to a maximum of approximately

150 mg. Care in keeping the stimuli near threshold made for greater refinement in response with avoidance of vigorous mass reactions. Acid stimulation applied by placing on the skin a speck of filter paper moistened in dilute (10%) acetic acid was also used in some instances. The adult newts were tested out of water. Motion pictures projected at reduced speed were used as an aid in analyzing the frog's wiping responses when these were too rapid to permit their specificity to be determined satisfactorily by direct observation.

Lateral-line fibers running alongside roots V and VII were generally transected along with the main nerve roots. No attempt was made, however, to study recovery of lateral-line function.

For microscopic examination of the brains and regenerated nerves the Bodian Protargol method was used. In order to conserve a diminished supply of pre-war Protargol, the following modification was adopted with satisfactory results. Instead of a 1.0% Protargol solution with copper, a 0.05% solution was used without copper. Approximately 0.5 cm^3 of 2.0% ammonium hydroxide was added per 100 cm^3 Protargol solution.

RECOVERY FOLLOWING CENTRIPETAL REGENERATION OF THE SEVERED ROOT V

Urodeles. From a ventral approach through the roof of the pharynx the root of cranial nerve V was completely sectioned intracranially on one side in 8 efts and in three aquatic newts. The nerve root was roughly broken and teased apart with finely pointed forceps. For two weeks thereafter the animals were unresponsive to tactile stimulation on the operated side within the cutaneous area indicated in figure 1.

Sensitivity began to return between the 16th and 34th days after operation, appearing earlier in the smaller animals. By the 72nd day all cases were exhibiting typical withdrawal responses to stimulation in the deafferented area. Different reactions could be elicited from different cutaneous points as follows: (a) depression of the head from the dorsal

tip of the snout, (b) elevation of the head from the ventral tip of the chin, (c) lateral withdrawal of the head from the edge of the jaw anterior to the eye, (d) combined lateral and downward withdrawal from a point intermediate between those of a and c, (e) withdrawal of the eye from the cornea and surrounding skin.

The recovered responses were quite normal in character. There was no indication in any animal that the sensory fibers had established atypical reflex connections in the trigeminal nucleus. With strong stimulation, eye withdrawal frequently accompanied head withdrawal even from points distant to

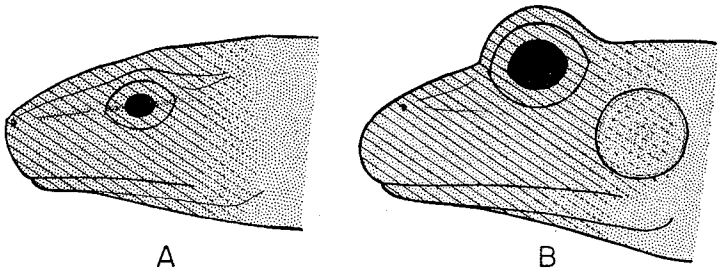

Fig. 1 Approximate extent of cutaneous insensitivity following section of root V in the newt (A) and frog (B). In the border area, indicated by broken lines, sensitivity is only partially reduced due to overlapping innervation. Considerable species and individual variation was found.

the eye. Likewise, under conditions of temporal summation it was possible to evoke a type of withdrawal response unusual for the point stimulated. However, the same is true of normal animals. When a near-threshold stimulus was used with sufficient intervals between stimuli to avoid temporal summation, it was possible to demonstrate consistently the differential and adaptive specificity of reactions from the different cutaneous loci.

The threshold of sensitivity had gradually recovered by the 72nd day until in the majority of cases it was not noticeably above that of the normal side. The recovered reflexes survived decerebration and were abolished in three cases so tested by resection of the regenerated fifth root.

Anuran tadpoles. Root V was similarly transected on one side from a dorsal approach in 17 tadpoles of Rana catesbiana during late larval stages. Four of these survived metamorphosis which occurred 3½ to 5 months after operation. Following metamorphosis stimulation of the cornea or upper eyelid on the operated side evoked an isolated retraction of the eyeball. Wiping reactions differentially directed in normal manner toward the stimulated point could be elicited consistently from the following 4 other loci within the affected area (see fig. 1): the tip of the snout, the ventral surface of the chin, the dorsal surface of the head between the eyes near the mid line, and the edge of the upper jaw half-way between eye and the tip of the rostrum.

These particular 5 loci were arbitrarily selected merely because they are widely separated and consequently the forelimb reactions involved are readily distinguishable. After cutting the roots of nerves VII, IX, and X a 6th test point could be added in the overlap area (see fig. 1) near the angle of the jaw. Presumably an intensive analysis would show that the functional specificity of loci within the trigeminal area is more refined than the foregoing might indicate and is field-like in nature with a continuous gradation from locus to locus rather than having any distinct division into 6, or more definite areas.

Unlike the newts the threshold of sensitivity was noticeably higher on the regenerated side in three of the frogs and remained so with only slight improvement in two cases for as long as 10 months after metamorphosis. In these frogs the recovered responses persisted after brain transection caudal to the optic chiasma and then disappeared after section of the regenerated root V.

Adult anurans. Unilateral intracranial division of root V was performed in 24 adult frogs (11 R. pipiens, 6 Hyla crucifer, two H. squirella, 5 H. cinerea) from a ventral approach through the roof of the pharynx. At 45 days after operation 6 of the 14 cases still alive (three H. crucifer, one

H. squirella, two R. pipiens) had begun to show signs of recovery of sensitivity in the deafferented area. At 100 days after operation evidence of recovery had appeared in 4 more cases (two R. pipiens, one H. crucifer, one H. cinerea). In two H. crucifer and one H. squirella, the three which showed best recovery, the corneal reflex and wiping reactions could be elicited separately by appropriately placed stimuli. In the remainder, however, recovery was so poor quantitatively that no satisfactory estimate could be made of its selectivity. Even in the best cases sensitivity remained conspicuously below normal on the operated side. Long temporal summation was required to elicit the responses and no reactions whatever could be evoked from many loci in the affected region.

In 11 additional R. pipiens the trigeminal root was merely crushed with forceps. Such crushing breaks and separates the nerve proper but leaves partly or entirely intact the outer connective tissue sheath which then serves as a guide for the regenerating nerve and helps prevent formation of scar tissue. The individual fiber channels within the nerve itself do not survive such crushing in these soft nerve roots as they frequently do in the tougher peripheral nerves of mammals.

Five of the 11 cases survived 7 to 11 months, but even under these more opportune conditions for regeneration they exhibited only meager evidence of recovery. At best the responses were difficult to elicit requiring long temporal summation. The corneal reflex and wiping responses were separately elicitable to some degree but the recovery was so poor quantitatively in these cases as in the preceding series that estimates of its quality could have little meaning. Further attempts to obtain regeneration in the adult anurans were thereupon abandoned.

On postmortem dissection and histological examination it was found that regeneration of fibers from the point of severance had been extremely poor or lacking. The poorness of recovery, therefore, may have been due entirely to the

low level of regenerative capacity rather than to any direct inability to form functional synapses. Apparently the nerve root V, like the spinal sensory roots (Sperry, '49), has less regenerative capacity than does the optic nerve in adult anurans. Intermediate success has been obtained with root VIII which displayed good regeneration in adult H. squirella (Sperry, '45b) but only feeble regeneration in H. cinerea and R. pipiens.

In the newts and in the frog tadpoles the central reflex relations were reestablished in an orderly systematic pattern. Under the conditions of regeneration this cannot be ascribed to any combination of mechanical and timing factors. The individual fibers become haphazardly intermixed in the nerve scar (see fig. 3, B, C). Furthermore, in the central nervous system there are no distinct channels comparable to the neurilemma tubes of peripheral nerves to guide the regenerating fibers to their terminals. Some longitudinal alignment of the substrate presumably survives in the white matter, but when the advancing root fibers enter the neuropil, they have to make their way to their respective terminals without the aid of any specific pathways.

Occasionally unexplained crossed responses were noted in 5 of the adult frogs. Stimulation on the operated side after regeneration evoked the corneal reflex or wiping reactions on the opposite instead of the stimulated side. It was found upon further testing that the responses could also be elicited sometimes in the other direction from the intact to the operated side. The consistency with which they occurred varied greatly in different individuals. Similar allesthetic reactions from the normal to the operated side have been observed following section of the dorsal roots of the hind limb. The cause of the phenomenon and whether it is related to any of the allesthesias in man (Bender et al., '48) remains to be discovered.

ROOT V CROSSED TO THE CENTRAL STUMP OF ROOT VII

Operation. In 8 efts and 7 aquatic newts root V was broken close to its entrance into the brain and the main division

of root VII was broken proximal to its ganglion. The peripheral end of V was then united to the central cut end of VII (see fig. 2). The ganglion of VII was extirpated in whole or in part and chips of cartilage were placed between the nerve union and the central stump of root V to help prevent undesired regeneration into the original pathways. In 7 cases an anterior ramus of VIII which runs close beside VII was also divided. During the following two weeks the animals were insensitive on the operated side to stimuli applied in the affected area. The insensitive area did not differ appreciably from that shown in figure 1A. The motor loss in these cases impaired somewhat but did not abolish the animals' ability to pick up and swallow live enchytrae worms and small pieces of beef and liver.

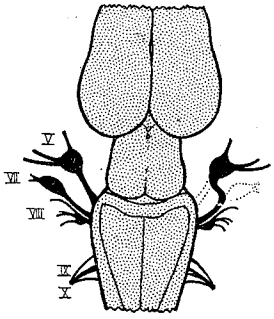

Fig. 2 Diagram of cross-union of nerve roots V and VII.

Definite responses from the deafferented cutaneous area began to reappear approximately 37 to 45 days after operation in the group of efts. The smallest efts were first to recover. By the 55th day after operation, 7 of the 8 efts had recovered sensitivity and regularly displayed the three differential types of head withdrawal: downward, sideward, and upward to stimulation on the top of the snout, side of the jaw, and ventral surface of the chin, respectively. Combined downward and lateral withdrawal from the dorsolateral area of the snout could also be elicited. In addition three of the 7 withdrew the eyeball to stimulation of the cornea and upper lid. The absence of the corneal reflex in the other cases was probably due to accidental division of the cranial motor nerve VI to the retractor bulbi muscle. This

nerve, which runs in the vicinity of root V, is so fine in these young animals that frequently it is not seen and thus is easily broken in the operation.

Recovery was delayed much longer in the adult newts. The corneal reflex began to reappear about two months after operation in the 6 cases still alive. It was another month before the other withdrawal reflexes were restored. By the end of the 4th month after operation the various cutaneous reflexes had become well established in 4 of the 5 animals which still survived. As in the efts the respones were appropriately directed with reference to the site of stimulation with no evidence of atypical central connections.

In general, recovery in a quantitative sense was not so good in either of these groups as it had been after straight regeneration of root V into its own central stump. Particularly in the adult newts sensitivity remained subnormal at many points and the reactions were usually weaker than those elicited from the unoperated side.

The operative site was reexamined for possible misregeneration of V into its own central stump on the 55th day after operation in the group of efts and on the 128th day in the aquatic newts. In only one eft was a distinct but very thin trigeminal root found emerging from its usual point. This root was severed and in all other cases forceps were passed through the space around the original exit point of V to destroy any diffuse unseen fibers that might have regenerated. The selective withdrawal responses of the head survived this operation without noticeable deterioration. The corneal reflex, however, was abolished in the efts and in one of the adult newts presumably by section of motor nerve VI which was even more difficult to avoid in the site of the scar than in the original operations. The recovered responses survived transection of the brain posterior to the optic chiasma in all cases and the responses were subsequently abolished by division of root VII in three efts so tested. Histological examination of the remaining animals further confirmed the fact that the root fibers of V had regenerated

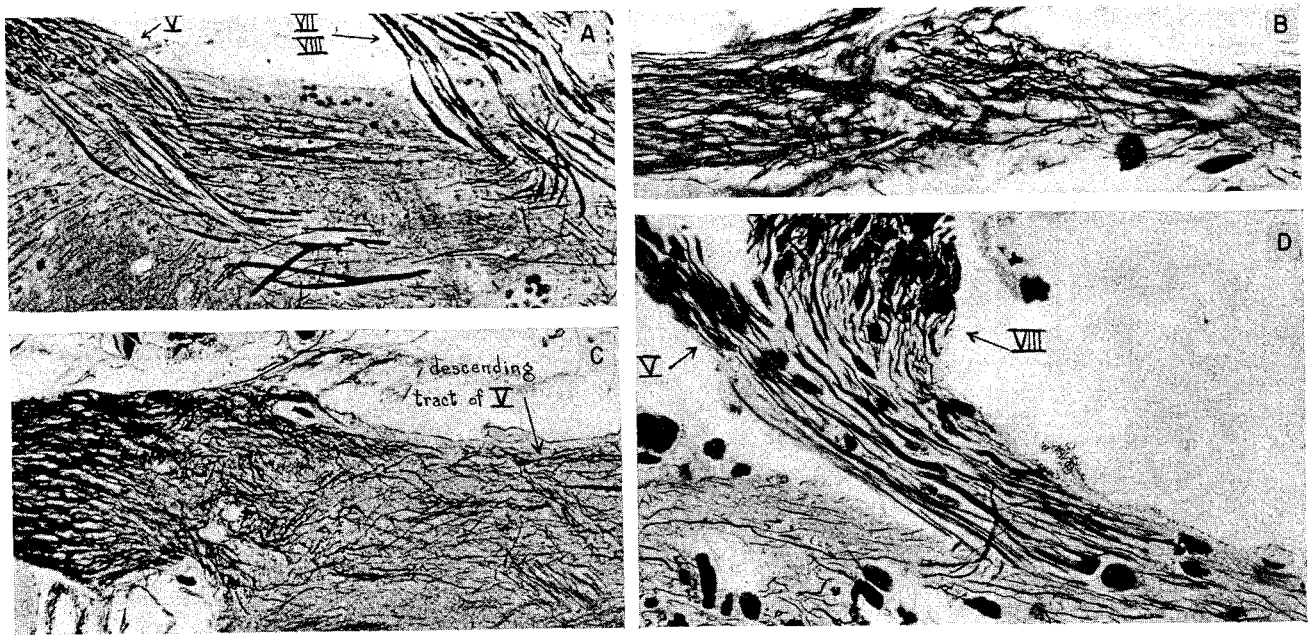

Fig. 3 Photomicrographs of horizontal sections through the regenerated V root and tract. Oriented with trigeminal ganglion out of view toward left and medulla oblongata toward bottom and right. (Sections cut at 10 μ and prepared by modified Bodian Protargol method.)

A. Fibers of root V entering medulla of frog tadpole. × 215.

B. Region of transection of V in eft. Distortion of fiber pattern in nerve scar is evident. × 340.

C. Same as (B) only in this case the transection was at entrance into brain. × 215.

D. Fibers of V entering brain via degenerated VII alongside VIII in adult newt. × 286.

into the brain via the seventh root pathway as intended (see fig. 3D). From Herrick's ('48) description of the normal central relations of the seventh root fibers and the trigeminal centers we may assume that the ingrowing fibers managed to reach trigeminal neuropil.

The conditions under which the central reflex relations were established in this group of animals, even more than in the preceding series, clearly eliminate any possibility that the orderly patterning of the central synaptic linkages could have been due to mere mechanical guidance of the ingrowing fibers, each type to its appropriate central terminals.

REGENERATION OF ROOT V AFTER PERIPHERAL CROSS-UNION OF OPHTHALMIC AND MANDIBULAR NERVES

Operation. In 13 efts and 8 aquatic newts the peripheral ophthalmic division of the trigeminal nerve to the dorsal surface of the snout was sectioned and its central end was apposed to the distal end of the divided mandibular nerve which supplies the lower jaw and chin (see fig. 4). The

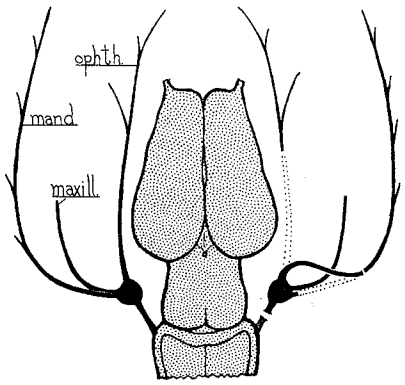

Fig. 4 Diagram of cross-union of ophthalmic and mandibular nerves plus transection of root V as described in text.

ophthalmic nerve was dissected free, cut distally, and reflected along the course of the mandibular nerve posterior to the eye. The central stump of the mandibular nerve was excised as far centrally as possible to help prevent regeneration into its own distal stump. The optic nerve was se-

vered to facilitate reflection of the ophthalmic nerve. The cut ends of the ophthalmic and mandibular nerves were merely apposed without suture or tubulation in the natural intermuscular channel of the mandibular trunk.

Signs of return of sensitivity began to appear between 10 and 17 days after operation in the different cases. The fifth root was then sectioned between 13 and 20 days after the nerve-cross operation. This was during the early stages of recovery in 14 cases and prior to any signs of recovery in the remaining 7. Thereafter no responses were elicitable for a period of approximately two weeks while the sectioned root V was regenerating.

It has frequently been supposed that growing nerve fibers have an initial tendency to form synapses in a diffuse, non-selective manner and that those connections which happen to produce adverse functional effects undergo atrophy, resorption, or degeneration while those which prove to be functionally adaptive are retained and reinforced. Establishment of synaptic associations on this principle following the ophthalmic – mandibular nerve – cross described should restore the normal response to stimulation in the mandibular area, i.e., elevation and withdrawal of the head. If, conversely, the animals should respond by depressing the head more strongly against a noxious stimulus, it would mean that the central reflex relations had been patterned on some basis other than that of functional adaptiveness.

Responses to cutaneous stimulation in the trigeminal area began to reappear between 13 and 30 days in different cases. After recovery had been well established, stimulation of the under side of the rostral third of the mandible between the chin and the eye regularly caused depression of the head instead of the normal elevation. The responses were variable in the adjacent cutaneous areas near the tip and along the caudal half of the mandible due apparently to the presence of overlapping innervation from neighboring intact nerves.

In 6 of the 21 cases no reversed reactions of the above sort could be evoked and in these the normal type of response was eventually recovered in varying degree. Upon examina-

tion under the dissecting microscope it was found that the nerve crosses in these 6 cases had been technically unsuccessful and that the mandibular nerve had succeeded in regenerating into its former channels. Accordingly these 6 animals were discarded from the experiments.

In the 15 successful cases (10 efts, 5 adults) stimulation of the corresponding region of the contralateral mandible evoked the typical elevation of the head in contrast to the depression on the operated side. Alternate depression and elevation could be evoked at intervals by stimulating alternately the intact and the operated sides. Nine of the efts were kept as long as 137 days after the initial signs of recovery. There still was no evidence of correction of the reversed reactions.

REFLEX MATURATION AFTER CONTRALATERAL CROSS-UNION OF THE OPHTHALMIC NERVES

Operation. The ophthalmic nerves were cut on each side and the central end of the right nerve was crossed to the distal end of the left nerve (fig. 5). The operation was performed in 20 tadpoles (12 R. catesbiana, three R. clamitans, 5 R. pipiens) in late larval stages all prior to the emergence of the forelimbs. In 6 cases a transverse strip of cranium was removed over the thalamus and the right nerve was

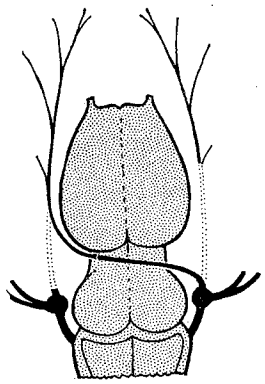

Fig. 5 Diagram of contralateral cross-union of ophthalmic nerves.

passed through this groove just posterior to the cerebral lobes. In the remainder the nerves were crossed dorsal to the intact cranial roof. The intended regeneration should result in the innervation of the left ophthalmic cutaneous field by the right ophthalmic nerve.

If the central organization of the localizing reflexes were predetermined by developmental forces, the wiping responses, after metamorphosis, ought to be directed at the wrong side of the snout upon stimulation of the left ophthalmic area. If, on the contrary, the central organization were acquired through function, the frogs might soon come to direct their wiping responses correctly toward the point stimulated. Eleven cases survived metamorphosis. In 9 of these (4 R. catesbiana, three R. pipiens, two R. clamitans) tactile stimuli applied in the left ophthalmic area elicted wiping responses of the contralateral limb directed toward the right ophthalmic area. Also the right eye was retracted instead of the left. When a small piece of filter paper dampened in dilute acetic acid was placed on the left side of the snout, the frogs repeatedly wiped at the wrong side failing to remove the paper. Resection of the trigeminal root on the reinnervated side extended somewhat the lateral border of the cutaneous area from which these crossed reactions could be obtained. The remaining two cases were discarded after an exploratory examination of the operative site revealed that the nerve crosses had been unsuccessful.

Six of the frogs died between 14 and 29 days after the first appearance of the crossed responses. The remaining three survived 4½ months after metamorphosis. No special effort was made to train any of the frogs to respond correctly. However, they were tested daily during the first two weeks after metamorphosis and thereafter at intervals which increased gradually up to approximately two weeks. In all cases the abnormal crossed reactions remained fixed throughout with no evidence of any functional correction.

In both this and in the preceding series the ophthalmic root fibers formed and maintained over long periods their

typical pattern of central reflex relations despite surgical rerouting of the peripheral fibers into foreign cutaneous areas and the non-adaptive functional effects thus produced. The results in both series indicate that the synaptic patterns requisite for cutaneous local sign are systematically predetermined in growth and regeneration in the amphibians and are not a product of functional adjustment.

DISCUSSION

To explain the orderly formation of reflex relations in the trigeminal sensory nuclei under the conditions of the foregoing experiments it is necessary to conclude that the sensory neurons supplying different cutaneous areas differ in character. The sensory root fibers associated with different cutaneous loci must somehow be distinguished from one another in the centers in order that their synaptic relations may be formed in the appropriate selective manner.

Furthermore, the nature of the localizing responses requires that the sensory neuron specificity correspond with the topography of the trigeminal cutaneous field. It must reflect the topographic interrelations of all cutaneous points. For example, neurons innervating loci far distant from one another must be less similar in their biochemical constitution than those supplying adjacent areas. Neurons innervating any given locus must be systematically related in their specificity to those of every other locus throughout the cutaneous field. It would seem impossible that this could be attained in the absence of a corresponding qualitative differentiation of the skin itself.

Conceivably the integument and trigeminal neurons might each undergo a parallel but independent differentiation. Attainment of the proper peripheral linkages under such circumstances would necessitate selective outgrowth of the sensory fibers each to its correct cutaneous locus. Linkages of the sort required could also be established through a relatively indifferent outgrowth and termination of the sensory fibers followed later by induction of specificity in the

fibers as a consequence of their connections with the differentiating cutaneous field. In harmony with this latter possibility is the conclusion of Weiss ('42) and Kollros ('43) that the cornea of an extra eye grafted to the ear region in amphibians is able to specify the fibers that innervate it and thereby bring these fibers into proper relation with the central mechanism of the lid-closure reflex. In the present experiments evidence that the integument can impose local specificity upon its nerve supply failed to appear in the results of crossing the ophthalmic nerve into mandibular skin. Study of this question is being extended, however, to larval and embryonic stages on the assumption that the neuronal specification may possibly have already reached an irreversible status in the post-larval Triturus.

In their implications regarding the devolopment and neural basis of cutaneous local sign the results are essentially similar to those obtained earlier in the hind limb region of the frog (Sperry, '49). Taken together the findings suggest that the development of cutaneous local sign depends upon a highly refined field-like differentiation of the entire integument plus a parallel differentiation of the primary sensory neurons. The specification of the sensory fibers, perhaps imposed in part by induction from the cutaneous field, would make possible an orderly, selective formation of reflex relations in the centers on a chemical affinity basis. This interpretation implies a correlated specificity among the second order neurons, which, in turn, must be distinguishable according to their various efferent relations in order that the invading root fibers may form the appropriate linkages. Considerable overlap must be presumed to exist in the central terminations of fibers supplying adjacent cutaneous areas.

This refined type of neuron specificity, the existence of which was first emphasized by Weiss with reference to the motor supply of the limb muscles ('28, '36, '41), has been found also in the motor nerves of the extrinsic eye muscles (Sperry, '47), in the proprioceptive (Sperry, '49; Weiss, '36, '41) and cutaneous (Sperry, '49) innervation of the limbs, in

the optic (Sperry, '43b, '44, '45a) and vestibular (Sperry, '45b) nerves, and in the tecto-bulbar and tecto-spinal tracts (Sperry, '48a) of amphibians; also in the preganglionic sympathetics of the cat (Langley, 1898) and in the visual system of teleosts (Sperry, '48b). Thus far no definite proof is available regarding the exact manner in which the peripheral fiber specificities determine formation of proper relations with the central mechanisms. It has been suggested (Sperry, '41, '43b, '49) that synaptic associations may be formed in the centers both in development and in regeneration in a selective manner on the basis of differential physico-chemical affinities and incompatibilities between the peripheral and central neurons. Synaptic connections of the intracentral association tracts (Sperry, '48a), likewise, have been assumed to be patterned on this principle.

Although this interpretation is the simplest we can see at present, a number of difficulties in its application will become apparent: First, any such scheme of selective central connections must allow for considerable plasticity in function and even for complete reversal of responses. For example, the withdrawal reflexes referred to above may be transformed into approach reactions if the animals are hungry and in the process of being fed. Secondly, direct central inhibition in reflex and integrative circuits (Lloyd, '46) seems to require a separate set of inhibitory connections. Establishment of both excitatory and inhibitory linkages on an interneuronal affinity basis introduces obvious complications for the hypothesis. Finally, the interpretation is less easily applied to central-peripheral adjustments of the sort recorded by Weiss ('28, '36, '41, '42) in which only peripheral connections are altered leaving the central linkages undisturbed. One must postulate that existing synaptic relations break down in the centers under the latter conditions and that new ones are formed. Some alternative theory which bases the selectivity of central-peripheral relations upon physiological resonance phenomena (Weiss, '28, '36,

'42) rather than upon selective structural relations may eventually prove more adequate.

The present experiments furnish no information regarding the additional dimension of differentiation among the trigeminal neurons required for the various sense modalities like pain, touch, and temperature. Presumably the local sign specificity would have to be superimposed upon this modal differentiation.

In any case genetic organization of the central sensoria mediating cutaneous local sign is obviously indicated with "education of sensory surfaces" in the sense of Holt ('31) being unnecessary. The fact that cutaneous localization can be improved to some extent by training in man and possibly in other mammals (Sperry, '43a, 45c) does not render unnecessary a basic inherent organization in the above sense.

SUMMARY

1. Centripetal regeneration of cranial nerve root V following complete transection resulted in an orderly restoration of cutaneous localization within the trigeminal area (8 eft and three adult T. viridescens, 4 tadpole R. catesbiana). Regeneration in several species of adult frogs was too poor to permit satisfactory estimation of the quality of functional recovery.

2. After cross-union of nerve roots V and VII, regeneration of the trigeminal root fibers into the brain over the pathways of the cranial seventh nerve resulted in orderly recovery of cutaneous local sign (7 eft and 4 adult T. viridescens).

3. Regeneration of the transected trigeminal root following peripheral cross-union of the ophthalmic and mandibular nerves resulted in recovery of reversed responses to stimulation of the ophthalmic-innervated mandibular area (10 eft and 5 adult T. viridescens).

4. Contralateral cross-union of the ophthalmic nerves in frog tadpoles previous to metamorphic emergence of the forelimbs resulted in the maturation of wiping reflexes di-

rected toward the wrong side of the head (4 R. catesbiana, two R. clamitans, three R. pipiens).

5. The results appear to eliminate mechanical guidance and functional adaptation as the factors responsible for the neural organization mediating cutaneous local sign in amphibians. They indicate the existence of a refined constitutional specificity among the cutaneous nerve fibers and in the integumentum itself. The patterning of synapses between sensory and central neurons is tentatively explained in terms of our chemoaffinity theory of synaptic formation.

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